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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/215,163	12/18/1998	JEFFREY R. STINSON	04995.0032-0	7721

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	**PAPER NUMBER**
1645	

NOTIFICATION DATE	DELIVERY MODE
09/25/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	09/215,163	STINSON ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,17-19,23,29,34-38,44,47 and 54-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,17-19,23,29,34-38,44,47 and 54-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 6/1/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed on 6-1-2007 are acknowledged. Claims 1, 19, 34-38, 44, 47 and 54-55 have been amended. Claims 2, 14, 20, 32-33, 39-43, 45-46 and 48-53 have been canceled. Claims 56-63 have been added. Claims 1, 17-19, 23, 29, 34-38, 44, 47 and 54-63 are pending and currently under examination.

Declaration

The Declaration by Dr. Hing Wong filed on 6-1-2007 has been considered.

Claim Rejections Withdrawn

The rejection of claim 41 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 is withdrawn. Cancellation of said claim has rendered the rejection moot.

The rejection of claims 1, 2, 14, 17-20, 23, 29 and 32-55 are rejected under 35 U.S.C. 102(a) as being anticipated by Edwards et al. (V110/11:113 page 113, 1997 – IDS) is withdrawn in light of the Declaration by Dr. Hing Wong filed on 6-1-2007.

Claim Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 17-19, 23, 29, 34-38, and 56-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 in view of Carter et al. (WO 94/04679) is maintained for reasons set forth in the rejection of claims 1-2, 14, 17-20, 23, 29 and 32-55 in the previous Office action.

Applicant argues:

1. The Office has failed on establish that one of skill in the art, in view of the 5,747,272 patent would be motivated to modify the teachings of claim 9, to arrive at the instant invention.

2. Applicants provide strong evidence of the non-obviousness of the instant invention.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1 and 2, patent 5,747,272 discloses the murine antibodies 11E10 and 13C4 in claim 9. Carter et al. disclose methods of humanizing murine antibodies and in order to reduce the side effects associated with anti-mouse immunoglobulins. Consequently, it would have been obvious for the skilled artisan to humanize the antibodies of patent 5,747,272 to minimize the side effects of murine antibodies. Since the process of humanization of murine

antibodies is well known in the art yielding predictable results, it is obvious for the skilled artisan to humanize any murine antibody.

35 USC § 112

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 17-19, 23, 29, 34-38, 44, 47 and 54-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized monoclonal antibodies **consisting of** the variable heavy and light chains of monoclonal antibodies 13C4 or 11E10 (**defined regions**), does not reasonably provide enablement for humanized antibodies "comprising the heavy chain and light chain variable reasons of containing at least part of a murine immunoglobulin variable regions as shown in Figure 3 (SEQ ID NO:21 or Figure 6 (SEQ ID NO:42), wherein the antibody specifically reacts with Stx1 or Stx2 antigen or portions of SEQ ID NO:42 or SEQ ID NO:44 (i.e. the variable light and heavy chains of monoclonal antibodies 13C4 or 11E10) for essentially the reasons set forth in the previous Office action in the rejection of claims 1, 2, 14, 17-20, 23, 29, 32-40 and 42-55. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

Applicant argues:

1. Applicant's have amended the claims to recite only the antibody species that the Examiner has indicated as allowable.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, the amended claims do not read on the antibody species that that were indicated to meet the enablement requirement. The specific species of humanized antibodies that meet the enablement requirement are those that contain the only (i.e. consist of) variable light and heavy chains of monoclonal antibodies 13C4 or 11E10. The instant claims recite the open claim language "comprising". As a single amino acid, even one that is distil to the binding epitope, can radically affect or ablate antibody binding, the instant claims are not deemed to be enabled for the full scope of the instant claims. It should be noted that the Examiner has not indicated any claim to be "allowable".

As outlined previously, undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

Breadth of the claims

The rejected claims are drawn to a genus of humanized antibodies, the members of which specifically reacts with the Stx1 or Stx2 antigen wherein the variable light and heavy chains of said antibodies comprise the variable light and heavy chains of the monoclonal antibodies 11E10

or 13C4.

Working Examples/Guidance of Specification

The specification fails to describe immunoepitopes against which the claimed antibodies are raised and must subsequently bind. The working examples disclose specific antibodies that meet the limitations of the instant claims. However, these "examples" are not sufficient to provide enablement for the full scope of the rejected claims. The specification is silent as to what specific "immunoepitope" confers said a given immune response.

State of the prior art and Unpredictability of the art

The specification outlines the materials and methods needed to make humanized antibodies utilizing the 13C4 or 11E10 monoclonal antibodies. However, the specification is silent on the sequences of the murine variable region required to confer function on the chimeric antibody the location (or sequence) of the immunogenic epitopes. Given the lack of guidance contained in the specification and the unpredictability in determining acceptable sequence variations, one of skill in the art could not make the broadly claimed invention without undue experimentation. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al

further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, Greenspan et al. (*Nature Biotechnology* **17**: 936-937, 1999), disclose defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of a directed immune response, the specification, as filed, is only enabling for only the specific antibodies disclosed in the specification that are produced from monoclonal antibodies13C4 or 11E10 (i.e. consist of the variable light and heavy chains of monoclonal antibodies 13C4 or 11E10).

Claims 23, 29, 44, 47, 54-55, 57 and 61-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions

comprising humanized monoclonal antibodies with the variable light and heavy chains of monoclonal antibodies 13C4 or 11E10 (**defined sequences**), does not reasonably provide enablement for pharmaceutical compositions comprising humanized antibodies "comprising the heavy chain and light chain variable reasons of containing at least part of a murine immunoglobulin variable regions as shown in Figure 3 (SEQ ID NO:21 or Figure 6 (SEQ ID NO:42), wherein the antibody specifically reacts with Stx1 or Stx2 antigen or portions of SEQ ID NO:42 or SEQ ID NO:44 (i.e. the variable light and heavy chains of monoclonal antibodies 13C4 or 11E10) for essentially the reasons set forth in the previous Office action in the rejection of claims 23, 29, 39-40 and 44-55. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

Applicant argues:

1. Applicant's have amended the claims to recite only the antibody species that the Examiner has indicated as allowable.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, the amended claims do not read on the antibody species that that were indicated to meet the enablement requirement. The specific species of humanized antibodies that meet the enablement requirement are those that contain the only (i.e. consist of) variable light and heavy chains of monoclonal antibodies 13C4 or 11E10. The instant claims recite the open claim language "comprising". As a single amino acid, even one that is distil to the binding epitope, can radically affect or ablate antibody binding, the instant claims are not deemed to be enabled for the full scope of the instant claims. It should be noted that the

Examiner has not indicated any claim to be "allowable".

As outlined previously, the specification only provides examples of humanized 13C4 and 11E10 antibodies, which are set forth in the rejection as being enabled. However, the specification is silent on how any other of the claimed antibodies would be used and equally silent on the efficacy of a given composition. Hence, since no evidence has been provided that illustrates or even suggests that the full breadth of the claimed pharmaceutical compositions are capable of eliciting a beneficial therapeutic response, one of skill in the art would not be able to make and use the claimed invention.

Written Description

Claims 1, 17-19, 23, 29, 34-38, 44, 47 and 54-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. Applicant's have amended the claims to recite only the antibody species that the Examiner has indicated as allowable.

The rejected claims are drawn to a genus of humanized antibodies, the members of which specifically reacts with the Stx1 or Stx2 antigen wherein the variable light and heavy chains of said antibodies comprise the variable light and heavy chains of the monoclonal antibodies 11C10 or 13 C4.

As outlined previously, the courts have recently decided in Randolph J. Noelle v Seth

Lederman, Leonard Chess and Michael J. Yellin (CAFC, 02-1187, 1/20/2004) that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See Enzo Biochem II, 323 F.3d at 965; Regents, 119 F.3d at 1568. Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen. Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier

filing date of his '799 patent application.

In the instant application, Applicant has failed to "fully characterize" the antigen (Stx1 and Stx2) to which the claimed antibody binds. The instant claims are drawn to all antibodies or fragments thereof with specificity to any Shiga toxin proteins generally, or Stx1 and Stx1 specifically, as long as said antibody comprises "at least a part of" a given immunoglobulin variable region. This includes Fab fragments that have limited immunological properties as compared to intact monoclonal antibodies. Consequently, since Applicant has not fully characterized the antigen to which the claimed antibodies bind, the written description requirements under 35 U.S.C 112, first paragraph have not been met.

The specification does not describe with any degree of specificity the Shiga toxin proteins to which the members of the claimed genus of antibodies must bind in order to achieve the desired immunological response, such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal

Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

As evidenced by Greenspan et al. (*Nature Biotechnology* **17**: 936-937, 1999), defining

epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows the epitope to which any given antibody binds can only be identified empirically. Even using a competition assay, the skilled artisan cannot determine whether an antibody binds the same epitope as another antibody because an antibody that competes with another does not necessarily bind the same epitope as the other; rather, one antibody may bind a spatially overlapping epitope to sterically hinder binding of the other. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of epitopes to which the members of the claimed genus of antibodies must bind, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of antibodies. Moreover, since the specification has not identified which amino acids of the genus of epitopes to which the members of the claimed genus of antibodies must bind, which are critical or essential to the binding, one skilled in the art would not recognize that Applicant had possession of the claimed invention at the time the application was filed.

In conclusion, only the specific antibodies disclosed in the specification that are produced from murine antibodies 13C4 and 11E10 (i.e. humanized antibodies whose variable light and heavy chains consist of the variable light and heavy chains of antibodies 13C4 and 11E10) meet

the Written description requirement.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1,17-19, 23, 29, 34-38, 44, 47 and 54-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spiers et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Carter et al. (WO 94/04679) and Tzipori et al. (U.S.2003/0082189 A1 – IDS) for essentially the reasons set forth in the previous Office action in the rejection of claims 1, 2, 14, 17-20, 23, 29 and 32-55.

Applicant argues:

1. There is nothing in the references of record that provides a basis for selecting either 13C4 or 11E10 as a candidate antibody for humanization to arrive at the defined antibodies as presently claimed.

2. There is nothing in Speirs or O'Brien that teaches, suggests, or motivates the skilled worker to use their antibodies in a therapeutic application to treat a Shiga toxin induced disease, much less to humanize these antibodies for that purpose.

3. Carter describes general methods of humanizing an antibody and fails to describe or even mention either the 13C4 or 11E10 antibody.

4. Tzipori fails to provide motivation to produce the claimed humanized 13C4 and 11E10 antibodies because Tzipori describes different antibodies and fails to even mention 13C4 and 11E10.

5. The 13C4 and 11E10 antibodies were known at the time Tzipori et al. was filed. Given that Tzipori et al. did not utilize them in his studies demonstrates that the skilled artisan would not choose to humanize 13C2 or 11E10.

6. As exhibited by Exhibit B, there is an unmet medical need for treating infections resulting from Shiga toxin producing bacteria and that Applicant's antibodies address this unmet need.

Applicant's arguments have been fully considered and deemed non-persuasive

With regard to Point 1, humanizing either the 13C4 or 11E10 monoclonal antibodies would necessarily result in humanized antibodies with the same binding specificity as the antibodies of the instant invention. Moreover, Applicant is reminded that one cannot show

nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant rejection the motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome.

With regard to Point 2, In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the use the claimed antibodies in a therapeutic application to treat a Shiga toxin induced disease) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Moreover, Applicant is reminded that the rejected claims are product claims and as such any intended use does not constitute a claim limitation. As the antibodies resulting from the combination of the cited references are the same as those of the instant invention, they would necessarily have the same binding affinities. Therefore, all the limitations of the instant claims are met. Finally, contrary to Applicant's assertion, Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome.

With regard to Points 3 and 4, Applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant rejection the motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific

for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome. Moreover, Tzipori et al. disclose that the anti-Shiga toxin antibodies are either human monoclonal antibodies or chimeric monoclonal antibodies (see paragraph [0004]).

With regard to Point 5, contrary to Applicant's assertion, the skilled artisan would, upon reading all the cited references, would elect to humanize the 13C4 and 11E10 antibodies. Applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant rejection the motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome. Moreover, in view of the KSR decision, since the process of humanization of murine antibodies is well known in the art yielding predictable results, it is obvious for the skilled artisan to humanize any murine antibody (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]).

With regard to Point 6, while the instant invention may "address" an unmet medical need, they have not been demonstrated to "satisfy" it as required by MPEP 716.04. Consequently, the rejection is deemed proper and is maintained.

As outlined previously, Spiers et al. and O'Brien disclose the 11E10 and 13C4 antibodies.

They differ from the instant invention in that they don't disclose humanized forms of said antibodies.

Carter et al. disclose the methods of producing humanized antibodies.

Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome (see abstract).

Consequently, it would have been equally obvious for one of skill in the art to employ the methodologies disclosed by Carter et al. to humanize the 13C4 and 11E110 antibodies in order to reduce the side effects associated with anti-mouse immunoglobulins since the process of humanizing a known antibody is well known in the art. One would have been motivated to humanize said antibodies in order to use them in the treatment methodologies disclosed by Tzipori et al.

One would have had a reasonable expectation of success, as humanizing antibodies is a well-established method within the art. Furthermore, though the sequences of said antibodies where not explicitly disclosed it would have been standard practice for one of skill in the art to obtain said sequences utilizing standard sequencing methods.

Claims 1, 17-19, 23, 29, 34-34, 44, 47 and 54-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spiers et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Shitara et al. (U.S. Patent 5,866,692) and Tzipori et al. (U.S.2003/0082189 A1 – IDS) for the reasons set forth in the previous Office action in the rejection of claims 1, 2, 14, 17-20, 23, 29 and 32-55.

Applicant argues:

1. There is nothing in the references of record that provides a basis for selecting either 13C4 or 11E10 as a candidate antibody for humanization to arrive at the defined antibodies as presently claimed.

2. There is nothing in Speirs or O'Brien that teaches, suggests, or motivates the skilled worker to use their antibodies in a therapeutic application to treat a Shiga toxin induced disease, much less to humanize these antibodies for that purpose.

3. Shitara describes general methods of humanizing an antibody and fails to describe or even mention either the 13C4 or 11E10 antibody.

4. Tzipori fails to provide motivation to produce the claimed humanized 13C4 and 11E10 antibodies because Tzipori describes different antibodies and fails to even mention 13C4 and 11E10.

5. The 13C4 and 11E10 antibodies were known at the time Tzipori et al. was filed. Given that Tzipori et al. did not utilize them in his studies demonstrates that the skilled artisan would not choose to humanize 13C2 or 11E10.

6. As exhibited by Exhibit B, there is an unmet medical need for treating infections resulting from Shiga toxin producing bacteria and that Applicant's antibodies address this unmet need.

Applicant's arguments have been fully considered and deemed non-persuasive

With regard to Point 1, humanizing either the 13C4 or 11E10 monoclonal antibodies would necessarily result in humanized antibodies with the same binding specificity as the antibodies of the instant invention. Moreover, Applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant rejection the

motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome.

With regard to Point 2, In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the use the claimed antibodies in a therapeutic application to treat a Shiga toxin induced disease) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Moreover, Applicant is reminded that the rejected claims are product claims and as such any intended use does not constitute a claim limitation. As the antibodies resulting from the combination of the cited references are the same as those of the instant invention, they would necessarily have the same binding affinities. Therefore, all the limitations of the instant claims are met. Finally, contrary to Applicant's assertion, Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome.

With regard to Points 3 and 4, Applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant rejection the motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome. Moreover, Tzipori et al. disclose that the anti-Shiga toxin antibodies are either human monoclonal antibodies or chimeric monoclonal antibodies (see paragraph [0004]).

With regard to Point 5, contrary to Applicant's assertion, the skilled artisan would, upon reading all the cited references, would elect to humanize the 13C4 and 11E10 antibodies. Applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant rejection the motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome. Moreover, in view of the KSR decision, since the process of humanization of murine antibodies is well known in the art yielding predictable results, it is obvious for the skilled artisan to humanize any murine antibody (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]).

With regard to Point 6, while the instant invention may "address" an unmet medical need, they have not been demonstrated to "satisfy" it as required by MPEP 716.04. Consequently, the rejection is deemed proper and is maintained.

As outlined previously, Spiers et al. and O'Brien disclose the 11E10 and 13C4 antibodies.

They differ from the instant invention in that they don't disclose humanized forms of said antibodies.

Shitara et al. disclose the methods of producing humanized antibodies.

Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome (see abstract).

Consequently, it would have been equally obvious for one of skill in the art to employ the methodologies disclosed by Shitara et al. to humanize the 13C4 and 11E110 antibodies in order to reduce the side effects associated with anti-mouse immunoglobulins since the process of humanizing a known antibody is well known in the art. One would have been motivated to humanize said antibodies in order to use them in the treatment methodologies disclosed by Tzipori et al.

One would have had a reasonable expectation of success, as humanizing antibodies is a well-established method within the art. Furthermore, though the sequences of said antibodies where not explicitly disclosed it would have been standard practice for one of skill in the art to obtain said sequences utilizing standard sequencing methods.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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ROBERT A. ZEMAN
PRIMARY EXAMINER
September 16, 2007